Update on Mental Health Issues in Patients With HIV Infection

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HIV infection remains a major world health problem more than 20 years after discovery of the virus. Mental disorders make individuals more vulnerable to behaviors that transmit HIV and interfere with HIV treatment adherence. The evidence supporting the need for optimal provision of mental health care in HIV clinics is mounting, along with evidence that these disorders can be treated successfully. Disorders of mental life include brain diseases (eg, depression, bipolar disorder, schizophrenia, and dementia), personality disorders, addictions, and psychologic disruptions, which contribute to the spread of the virus through their influence on behavior. However, although evidence exists that successful treatment of co-occurring mental disorders leads to improved HIV outcomes, integrated mental health care in HIV clinics remains grossly suboptimal.

Introduction

HIV infection remains a major world health problem more than 20 years after discovery of the virus and identification of transmission routes and prevention methods. Psychiatric disorders are a risk factor for infection and for poor HIV outcomes, and a consequence of the action of the virus on the brain and the immune system. We assert that the lack of coordinated treatment of psychiatric risk factors for HIV infection and transmission contribute to the ongoing epidemic.

Psychiatric conditions related to HIV infection are often assumed to be the inevitable psychologic consequence of being infected by the virus. A period of grief-like psychologic disruption occurs after the notification that a person has a potentially fatal and socially stigmatizing condition [1]. For many patients, this passes without clinical attention, but may lead to increased stress, substance use, and self-destructive behavior. The psychologic problems caused by diagnosis are only a part of the complex comorbid psychiatric conditions that play a role in acquiring HIV infection and in preventing adequate treatment response.

We use the diagnostic rubric proposed by McHugh and Slavney [2], an approach that has been particularly useful in integrating mental health care with medical care. In this article, we discuss conditions thought of as diseases of the brain (depression, bipolar disorder, schizophrenia, and dementia), disorders of behavior (eg, addictions), disorders emerging from dimensional traits (personality disorders and retardation), and disorders caused by psychologic reactions to aversive life experiences.

Psychiatric Diseases

Major depression in patients with HIV disease

Many patients in the HIV clinic have a depressed mood, but not all have major depression. *Major depression* may be best conceptualized as the result of brain dysfunction or a brain lesion, whereas *demoralization* describes a psychologic reaction to life stresses, which if severe enough may produce disorder [3]. Patients with more advanced HIV disease are at higher risk for major depression, with prior history of psychiatric disorder being the most important predictor of a major depression episode during the HIV-infected period [4•].

Prevalence of major depression in HIV-positive patients is 19% to 43% [5•,6]. The breadth of the spread represents a central problem in how major depression is ascertained. The issues for accurately ascertaining the diagnosis of major depression are complex, but studies show considerable variability, partly because of disagreements about the definition of major depression, and partly because of the methods for performing surveys [7]. For example, the Epidemiological Catchment Area (ECA) survey found a lifetime prevalence of 4.9% for major depression, whereas the National Comorbidity Survey (NCS) found a lifetime prevalence of 17.1%. This degree of disagreement in two carefully designed general population studies underlines the difficulty of obtaining an accurate estimate of major depression, but also reflects the problematic nature of diagnosing major depression in the HIV clinic [8]. The diagnosis can be assigned using rigid criteria assessed in a structured interview (generating data with

higher reliability but of questionable validity), or through a clinical interview by an experienced psychiatrist, which takes longer and is more expensive. Despite these issues, it is clear that depression is underrecognized and undertreated no matter which methods are used [9].

One barrier to accurate clinical diagnosis is that the typical features of major depression (eg, low mood, diminished sense of well-being and self-attitude) also may occur in grief or may be symptoms of the illness or side effects of medications. We have found the most useful diagnostic feature is the presence of anhedonia—patients do not experience pleasure or satisfaction from things or activities they formerly enjoyed. Patients can feel sad, flat, devoid of emotions, or empty. They often describe waking up early in the morning and having difficulty falling asleep again. In contrast to patients with major depression, demoralized patients can often tell that their sadness is a result of an event or a circumstance and can feel normal when distracted from their grief.

Treatment of major depression in HIV appears similar to treatment in non–HIV-infected patients. Numerous antidepressant trials showed good efficacy, with results similar to those in patients not infected with HIV [10]. No single antidepressant was proven superior in treating HIV-positive patients. Clinicians can choose antidepressants based on side-effect profiles, prescribe low doses of the chosen medication, and slowly titrate up to a full dose or therapeutic serum level to minimize side effects.

Non–medication-based treatments have been studied in several well-controlled clinical trials. Although some are difficult to compare with medication trials because of selection and methodology, many showed positive results. The group psychotherapy–based treatments were reviewed in an excellent meta-analysis by Himelhoch et al. [11].

Although providers may be concerned with the potential interaction of antidepressants and antiretrovirals, treatment of depression is critical for several reasons. First, major depression is associated with nonadherence to highly active antiretroviral therapy (HAART) [12,13]. Second, depressive symptoms were shown to decrease the immune response in HIV-positive individuals. Alciati et al. [14••] showed that number and percentage of natural killer (NK) cells were lower in depressed than in nondepressed HIV-positive patients, and the depression-related NK cell changes could not be modified with HAART. However, these changes can be reversed with the resolution of a depressive episode [15]. Finally, if interactions are a concern, it is relatively easy to monitor the blood levels of all psychotropic medications. Drug interactions for antidepressants were reviewed recently [16,17].

Bipolar illness in patients with HIV disease

Patients with bipolar disorder may experience depressive episodes (similar to those described earlier) and manic episodes. Mild mania (hypomania) presents with elevated energy, increased self-attitude and vital sense, and decreased sleep. Patients often feel as if their thoughts are "racing" and demonstrate pressured speech. Untreated hypomania may progress to mania or develop into depression. Mania lies at the extreme end of the spectrum of elevated mood states and is distinguished from hypomania by the presence of psychotic features. At times, manic patients are unable to express themselves because their ideas change too quickly and have no apparent connections between them ("flight of ideas"). Patients may have delusions of grandiosity, guilt, or worthlessness. Paranoid delusional thoughts and hallucinations are also common.

In the early years of the HIV epidemic, many patients late in the course of illness developed atypical manic states, a condition described as *AIDS mania*. AIDS mania is a secondary mania characterized by older than average age of onset, greater cognitive impairment, and lack of previous personal or family history of mania [18]. Patients typically present with irritable mood rather than euphoria, and increased agitation and activity. They can have delusional beliefs that they are cured or have discovered a cure for HIV disease. Zidovudine (azidothymidine, AZT), particularly at doses higher than 1.2 g/d, was sometimes associated with the development of manic episodes, and occasionally abacavir or efavirenz can induce a manic episode [19–21]. Acute mania and mixed states are usually treated with mood stabilizers and antipsychotic medicines. Lithium is the best-studied mood stabilizer, but it has a narrow therapeutic window and at doses required for mania has considerable side effects. Lithium levels must be monitored even more carefully in AIDS patients because their lithium blood levels can fluctuate very rapidly. Divalproate sodium, another mood stabilizer, may produce liver toxicity; therefore, blood levels and liver function must be monitored. The efficacy of carbamazepine as monotherapy was shown in a large, placebo-controlled study [22]. Lamotrigine has proven useful in treating bipolar disorder, and is well tolerated even by elderly patients [23]. Because it takes time for mood stabilizers to reach therapeutic serum levels, antipsychotic agents can be useful because their effect is more immediate. Antipsychotic agents have increasingly proven useful in adjunctive management of bipolar disorder and, in some studies, as monotherapy.

Treatment of AIDS mania has been a great challenge, but with the advent of HAART its prevalence is greatly reduced. Patients are far more medically ill, and the use of traditional mood stabilizers such as lithium and valproic acid is problematic, resulting in usual treatment with low doses of antipsychotic agents. The best approach has been to treat the underlying HIV disease, and the introduction of HAART produces the best results. Ferrando and Nims [24] successfully treated HIV-associated mania using bilateral electroconvulsive therapy in addition to HAART.

Schizophrenia in patients with HIV disease

The characteristic features of schizophrenia—hallucinations, delusions, thought disorders, and cognitive

deficits—can be found in illnesses other than HIV disease and create diagnostic complexity. As a result, some studies use the term *chronic mental illness* to encompass patients with schizophrenia, severe bipolar disorder, and unclassified chronic psychoses.

Several studies have shown that HIV prevalence is higher in patients with schizophrenia, and schizophrenia patients clearly have increased risk behaviors. Schizophrenia is strongly associated with substance abuse and high-risk sexual behaviors [25–28]. Himelhoch et al. [26] showed that although substance abusers with schizophrenia were 22% more likely to have HIV infection compared with the general population, schizophrenic patients without substance abuse disorder were 50% less likely to have HIV. This finding suggests that the social isolation and diminished ability for interpersonal relationships may be protective for individuals with schizophrenia.

The treatment of HIV-positive schizophrenia patients remains the same as for non-HIV patients. Given that HIV-positive schizophrenia patients are at risk for nonadherence, close monitoring and cooperation between mental and medical teams are highly recommended. Adherence to atypical antipsychotic agents in an HIV-infected population was found to be greater compared with older "typical" agents, probably because atypical agents have fewer side effects [29]. Because many schizophrenia patients have substance use disorders, it is important to screen carefully for substance use, treat it, and use psychosocial interventions to prevent relapses [30].

HIV-associated dementia

Like Parkinson's and Huntington's disease dementias, HIV-associated dementia (HAD) is categorized as subcortical dementia. Neuropathologies of HAD include loss of white and gray matter, particularly in the basal ganglia and posterior cortex [31], and a high degree of neuroinflammation in the hippocampus and basal ganglia [32]. The lack of HIV within neurons suggests that HIV does not directly infect neurons but kills them indirectly by infecting and disrupting functions of macrophages and microglia, which in turn release cellular and viral toxins [33]. Even though HIV can be detected in cerebrospinal fluid (CSF) in almost every HIV-positive individual at any stage of infection, only about 15% of patients develop HAD. In contrast to the numbers of HIV-infected cells, the amount of proviral DNA harbored by monocytes and macrophages and the presence of monocytes and microglia in the brain correlate well with HAD [34,35]. The putative risk factors for HAD are low CD4 cell count (< 200 cells/mm^3 is strongly predictive of HAD) and the presence of a previous AIDS event [36]. In addition, recreational drugs (eg, cocaine or methamphetamine) can exacerbate the neuropathogenesis of HIV [37,38].

Clinically, HAD presents with cognitive, affective, and motor dysfunctions. Early symptoms may be subtle (minor problems with reading, comprehension, memory, and mathematical skills) and can be misdiagnosed as illness or fatigue. Because of basal ganglia involvement, patients are more likely to experience movement and affective disorders. The movement problems at early stages may be subtle, such as slowing of fine repetitive movements, occasional stumbling while walking, and/or slight tremor. Examination findings include impaired saccadic movements, postural instability, diffuse hyperreflexia, dysdiadochokinesia, and frontal release signs.

Apathy is a common early syndrome and can be treated with low-dose stimulants. Patients with major depression, a common concomitant diagnosis, typically present with irritable mood and anhedonia. Depression can be treated with standard antidepressant therapies. Letendre et al. [39] suggest that serotonin reuptake inhibitors can reduce HIV replication in CSF in addition to improving neuropsychologic performance.

Currently, no specific treatment exists for HAD, so efforts concentrate on antiretroviral therapy. Letendre et al. [40••] assigned central nervous system penetration-effectiveness scores of 0 (low), 0.5 (intermediate), or 1 (high) to antiretrovirals, and concluded that a combined score below 1.5 correlated with higher CSF viral loads. Although current guidelines recommend initiating HAART when the $CD4^+$ count falls below 350 cells/μL^3, some clinicians wait longer because of adherence issues or other factors. Muñoz-Moreno et al. [41] argue that postponing initiation of therapy until CD4 counts drop to 300 cells/μL^3 may increase the risk of HIV-associated neurocognitive impairment. It is not yet clear whether these findings extend to other psychiatric conditions.

Delirium

Delirium is a state of global cerebral dysfunction caused by a major insult to the individual. Patients diagnosed with delirium—a marker of serious illness—have increased mortality. Studies in the pre-HAART era found high rates of delirium in hospitalized patients (30%–57%), and patients with a diagnosis of delirium have increased mortality [42]. The hallmark features of delirium are altered level of consciousness, difficulty with attention, confusion, trouble concentrating, and sleep-wake cycle abnormalities [43•,44].

The first step in treating delirium is identifying and removing the underlying cause as soon as possible. This can be difficult because the etiology is often multifactorial. Diagnosing delirium can be challenging, because hypoactive, disoriented delirium can be mistaken for depression, whereas hyperactive, agitated delirium can be mistaken for psychosis or dementia. Moreover, diurnal variations in delirium can be confusing because a patient may seem normal in the morning, but become agitated and difficult to care for at night ("sundowning"). A series of Mini-Mental State Examinations, careful history and physical examination, laboratory tests, review of medications, and electroencephalogram are essential for diagnosing delirium.

The second step is to orient the patient by maintaining a normal diurnal variation of light cycles and providing accurate clocks, calendars, and frequent verbal reorientation. Glasses and/or hearing aids should be provided when needed to minimize sensory impairment. It may be necessary to manage agitation using the lowest possible doses of high-potency antipsychotics. The use of benzodiazepines is controversial because they may worsen the delirium, but benzodiazepines are essential for deliria due to alcohol or benzodiazepine withdrawal.

Personality in Patients Infected With HIV

The terms *temperament* and *personality* are often used interchangeably, but for our purposes we define temperament as the *underlying natural response to stimuli*, and personality as the *expected behavioral response to stimuli* that an individual displays as the result of both temperament and learning.

Personality represents the total of a person's individual traits, and varies within the general population [45]. Many theories describe temperament in terms of dimensions of extroversion-introversion and stability-instability [46,47]. The dimension of *extroversion-introversion* refers to an individual's tendency to respond to a stimulus with excitation or inhibition. Extroverts respond with excitement; they are present-time oriented, feeling-directed, and reward-seeking. Feelings dominate thoughts in these individuals. Their primary concern is the immediate emotional experience: they want to feel good and they want it now. Introverts, on the other hand, respond to a stimulus with inhibition. They are future- and past-oriented, thinking-directed, and consequence-avoidant. An introvert avoids activity that might have adverse effects in the future, even when it provides immediate gratification.

The dimension of *stability-instability* refers to degree of emotional lability. Stable individuals are aroused slowly and minimally and require a large stimulus to produce an emotional response. Conversely, unstable individuals respond rapidly to a stimulus and have intense emotions that can be provoked by modest stimulation. Juxtaposition of the two personality dimensions gives us four personality types: unstable extrovert, stable extrovert, unstable introvert, and stable introvert.

Of these four temperaments, *unstable extroverts* are the most likely to engage in high-risk behaviors. These individuals act on feelings, with little regard to consequences. Unstable extroverts are more vulnerable to substance use because alcohol and drugs provide immediate rewards and relief [48]. In their view, pleasure is a bigger issue than safety; therefore, unstable extroverts are less likely to use condoms (because they diminish pleasure) and more likely to become injection drug users (because this provides a more intense experience).

Stable extroverts are also present-oriented and pleasure-seeking, but it is not their drive that makes them engage in high-risk behaviors. Instead, they may be too optimistic and believe that they cannot get infected. Although consequence-avoiding introverts are better protected by their personalities, they can still engage in high-risk activities because drugs and sex provide relief from demoralization or depression.

The same extroverted patients who are more inclined to engage in high-risk activities are more difficult to treat once infected. HAART adherence issues are more common in extroverted and unstable patients. These patients often have good intentions, but have difficulty following a rigid routine and tolerating uncomfortable side effects.

Because most health care providers are introverts, they often find treating extroverted and/or unstable patients challenging. Five principles of a cognitive-behavioral approach have proven effective when dealing with such patients: focus on thoughts and not feelings, use a behavioral contract, emphasize constructive rewards, use relapse prevention techniques, and coordinate with medical care providers.

Substance Abuse and Addiction in HIV Disease

Untreated drug dependence is a serious obstacle to the prevention and treatment of HIV infection. Injection drug use (IDU) is the main concern because it affects not only individuals who inject drugs, but also those who have sex with IDUs. However, other substance use also may promote high-risk behaviors.

Factors that initiate and sustain substance abuse are multiple and complex. Psychiatric and psychologic disorders, social acceptance, genetics, and certain medical problems that result in chronic exposure to narcotics can play a role in addiction. Psychiatric disorders not only predispose patients to substance abuse, but also make them more vulnerable to HIV infection [49]. Unstable extroverts are more willing to experiment and are more sensitive to the rewards drugs offer. Introverts are better protected by their consequence-avoiding personalities, but they may use drugs and alcohol to self-treat affective disorders such as depression.

Cohort studies consistently show poorer survival in substance users than in those without substance use or whose substance use is in remission [50,51]. This is true for IDU and those who use other illicit dugs. Cocaine use and amphetamine use also were associated with decreased adherence and poor outcome [52]. Marijuana use was exceptional in one study in which it was used to treat nausea, but had a detrimental effect in another study [53,54]. Alcohol use is also associated with decreased adherence and poor virologic outcome [55].

Drug users with HIV face multiple challenges while trying to access and adhere to treatment. Wood et al. [56] reviewed sociopolitical, individual, and provider-based barriers. Despite concerns to the contrary, it has been shown that IDUs and non-IDUs have similar resistance rates [57].

Treatment of HIV-positive drug users consists of several steps. 1) Induction of the patient role is often the most challenging step. Usually, addict and provider have different goals. The patient wants to feel better, whereas the physician wants the patient to get better even if the recovery process is uncomfortable. The idea is to help the patient slowly embrace recovery despite being uncomfortable. 2) Detoxification is an important and often unpleasant step. Benzodiazepine, barbiturate, and alcohol withdrawal can be life threatening and should be done in an inpatient setting. 3) Comorbid psychiatric conditions can be hard to diagnose in HIV-positive addicts, but should be treated whenever possible because the prognosis for both diseases is poor if left untreated. 4) Long-term treatment is best achieved by an integrated approach that provides structure to these patients, who are prone to relapse. Maintenance involves group therapy, therapy, and plans for relapse prevention, contingency management, and adequate pharmacologic therapy.

Psychologic Problems in Patients Infected With HIV

Psychotherapy and HIV

Some HIV-specific psychotherapeutic issues are pretest, test, and posttest counseling and risk behavior reduction in patients at risk or infected with HIV. Pretest counseling involves explaining the meaning of positive and negative test results and counseling on risk reduction. HIV-positive patients require additional tests, such as CD4 counts, HIV RNA loads, and resistance testing, each of which must be explained to patients. HIV diagnosis, disease progression, transition to AIDS, or detection of resistance are traumatic events that can provoke intense psychologic reactions in many people, so it is important to have psychologic interventions available at that time. Even if the test results are negative, posttest counseling is important for ongoing HIV education and counseling. Although posttest counseling can reduce further transmission of the virus, in their study Desai et al. [58] found that 42% of outpatients with serious mental illness like schizophrenia or bipolar disorder had never been tested for HIV, and of those tested, 51% had not received posttest counseling.

Many psychosocial intervention studies focus on primary prevention of infection in HIV-negative individuals. According to the Centers for Disease Control and Prevention, men who have sex with men (MSM) accounted for 71% of all HIV infections among male adults and adolescents in 2005. Interventions with this subgroup have shown variable positive impacts. Dilley et al. [59] showed that single-session personalized cognitive counseling intervention decreased unprotected anal intercourse in MSM by 60%, whereas Williams et al. [60] found that condom use increased by 23% after brief HIV risk-reduction interventions in street-based male sex workers.

The most important aspect of HIV treatment is a patient's adherence to HAART. Because psychiatric disorders can negatively impact adherence to treatment, physicians should screen for and treat these conditions with appropriate medications and psychotherapy. Meta-analysis of randomized, double-blind, controlled trials of group psychotherapy found it efficient in reducing depressive symptoms among HIV-positive patients [61•]. Cognitive-behavioral stress management training has also been shown to improve quality of life and potentially enhance the effectiveness of HAART on viral load suppression in combination with medication-adherence training [62,63].

Post-traumatic stress disorder in patients infected with HIV

Sexual assault in childhood may be related to post-traumatic stress disorder (PTSD), and is associated with an increase in HIV risk behaviors such as unprotected sex, sexual promiscuity, sex under the influence of alcohol and drugs, and sex trading [64]. Severe sexual abuse and sexual assault during childhood have been shown to be more prevalent in HIV-positive incarcerated women with lifetime PTSD than in those without PTSD. They are also more likely to have been arrested for prostitution and engage in risky sexual behavior and intravenous drug use than those without PTSD [65]. The relationship between HIV risk behavior and PTSD is complicated. It is not clear whether HIV risk behaviors such as substance abuse and/or prostitution predispose women to trauma and thus to PTSD or, conversely, whether women who have experienced childhood trauma develop PTSD that predisposes them to HIV risk behaviors.

Many individuals who develop PTSD following a traumatic event also develop depression. It is not yet clear whether PTSD directly affects adherence to HAART or whether adherence problems in this population are related to increased rates of major depression [66]. Depressive symptoms are also associated with lower CD4 cell counts and incompletely suppressed viral load [67]. Substance abuse is another common comorbid disorder that can adversely affect treatment. In clinical populations, 25% to 50% of patients have a dual diagnosis of PTSD and substance-use disorder. Addressing coexisting depression or substance abuse is paramount.

Receiving the diagnosis of HIV infection is almost always experienced as traumatic. In one study, 13% of young adults reported diagnosis-related PTSD, and another 20% showed posttraumatic stress symptoms [68]. Health care providers should keep in mind that receiving the initial diagnosis of HIV and worsening of the health status are traumatic experiences, and watch for demoralization. Treatment of PTSD should emphasize rehabilitation and function and include evaluation of other psychiatric conditions such as depression, substance abuse, and personality disorder. Simultaneous treatment of both disorders tends to be more effective and practical.

Conclusions

HIV disease is a viral illness that is transmitted by specific behaviors, all of which are either associated with or the direct result of mental illness. Model clinics that attempt to integrate treatment for mental illness, addictions, and HIV in one setting have shown promise for better outcomes [69,70]. The complexities of stopping this epidemic involve a realistic effort to treat psychiatrically ill patients before they become infected, and treating those infected to improve their lives and prevent further spread of the infection.

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